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(54) PHARMACEUTICAL COMPOSITIONS CONTAINING AMINOBENZANILIDES

(71) We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, Michigan, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

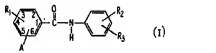
This invention relates to compositions containing known aminobenzamides for which anticonvulsant properties have now been discovered.

The following 2 - aminobenzanilides have been described previously: 2 - aminobenzanlide (Beilstein 14, 320; 14—11, 210); 2 - amino - o - benzotoluidine (Beilstein 14, 321); 2 - amino - N - methyl - *m* - toluanilide [J. Chem. Soc., 4110, (1959)]; 6 - amino - *m* - toluidides [J. Ind. Chem. Soc., 33, 365, (1956)]; and 2 - amino - 2',6' - benzoxylidene (Bull. Soc. Chim. France, 1962, 487). None of the above described compounds have been described as possessing anticonvulsant, sedative or muscle relaxant properties.

U.S. Patent Specification No. 3,443,833 described the use of 2 - amino - 4' - (diethylamino) - 2' - methylbenzanilide as an anticonvulsant.

In our Application No. 14543/74 (Serial No. 1459141), we have described and claimed certain novel aminobenzamides related to those of the present invention.

According to the present invention, pharmaceutical compositions are provided which comprise an aminobenzamide, as an active ingredient, in association with a pharmaceutically acceptable sterile liquid or solid carrier, in which the aminobenzamide is a compound of the formula



(I)

wherein R_1 and R_2 are the same or different and are each hydrogen or lower alkyl; R_3 is lower alkyl; and A is amino or a monovalent group of the formula —NHY wherein Y is the acyl radical of a hydrocarbon carboxylic acid having from 2 to 18 carbon atoms, with the provisos that

(i) when R_1 is hydrogen, A is not 4-amino or 2-NHY;

(ii) when R_1 is alkyl, A is amino; and

(iii) when R_1 is 3-methyl, A is not 2-amino.

Compositions within this invention are useful as mild sedatives and muscle relaxants in treating mammals, including humans. They are particularly useful anticonvulsants in that they show a high order of anticonvulsive activity coupled with a relatively low order of toxicity and only mild sedative properties. This makes their use particularly advantageous for the long term treatment of, for example, human epilepsy, since many of the prior art medicaments for treating epilepsy sedate the patient to an undesirable degree, or possess other unwanted side effects at effective anticonvulsant dosage levels.

Compounds within this invention are particularly advantageous anticonvulsants in that they show anticonvulsant activity of the order of at least 2 to 3 times that of diphenylhydantoin or 2 - amino - 4' - (diethylamino) - 2' - methylbenzanilide, both of which are widely known anticonvulsants. At the effective dosage levels of compounds used in compositions of this invention, fewer undesirable side effects are found than hitherto.

In this specification, "lower alkyl" means alkyl of one to 6 carbon atoms i.e. methyl,

ethyl, propyl, butyl, pentyl, hexyl, or an isomeric form thereof.

The term "acyl radical of a hydrocarbon carboxylic acid of from 2 to 18 carbon atoms" means a monovalent radical of the formula ECO— wherein E is hydrocarbyl of from one to 17 carbon atoms, and which is obtained on removal of the hydroxyl group from a hydrocarbon carboxylic acid. Illustrative of acyl radicals of a hydrocarbon carboxylic acid are the acyl radicals or (a) saturated or unsaturated, straight or branched chain aliphatic carboxylic acids such as, for example, acetic, propionic, butyric, isobutyric, *tert*-butylacetic, valeric, isovaleric, caproic, caprylic, decanoic, dodecanoic, lauric, tridecanoic, myristic, pentadecanoic, palmitic, margaric, stearic acrylic, crotonic, undecylenic, oleic, hexynoic, heptynoic and octylnoic acids; (b) saturated or unsaturated alicyclic carboxylic acids such as, for example, cyclobutanecarboxylic, cyclopentanecarboxylic, cyclopentenecarboxylic, methylcyclopentenecarboxylic, cyclohexanecarboxylic, dimethylcyclohexanecarboxylic and dipropylcyclohexanecarboxylic acids; (c) saturated or unsaturated alicyclic aliphatic carboxylic acids such as, for example cyclopentaneacetic, cyclopentanepropionic, cyclohexanebutyric and methylcyclohexaneacetic acids; (d) aromatic carboxylic acids such as, for example, benzole, *o*-, *m*- or *p*-toluic naphthoic, ethylbenzoic, isobutylbenzoic and methylbutylbenzoic acids: and (e) aromatic aliphatic carboxylic acids such as, for example, phenylacetic, 3 - phenylpropionic, phenylvaleric, cinnamic, phenylpropionic and naphthylacetic acids.

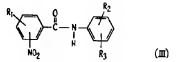
The term "convulsion" is used herein as meaning the violent involuntary contraction or repeated contractions of the voluntary muscles.

The term "seizure" is used herein as meaning the physical affliction characterised by transient clouding of consciousness, generally associated with a disturbance in the electrical activity of the cortex of the brain. Illustrative of such seizures are those associated with petit mal epilepsy.

The term "epilepsy" is used herein in its broadest sense, for example, as inclusive of grand mal, petit mal, and psychic equivalent or psychomotor attacks.

The term "effective amount" as used herein means the minimum quantity which prevents or blocks a convulsion or seizure of the type previously defined. In general, an effective amount is from 0.5 to 5.0 mg. of the compound per kilogram of body weight of the mammal to be treated.

Compounds of formula (1) above wherein A is amino can be prepared by reduction of the corresponding nitrobenzanilide of the formula



(III)

wherein R_1, R_2 and R_3 are as defined above.

The reduction of compounds (III) may be carried out by any of the well known methods for reducing a nitrobenzamide to the corresponding aminobenzamide. A convenient method is by catalytic hydrogenation.

The catalytic hydrogenation of compounds of formula (III) is readily carried out by reacting the nitrobenzamide (III) with hydrogen in the presence of an inert organic solvent and a hydrogenation catalyst.

The term "inert organic solvent" as used herein means an organic solvent for the reactants which does not react with the reactants or inerfere in any way with the desired course of the reaction. Illustrative of inert organic solvents are aliphatic organic solvents such as n-hexane and cyclohexane. aromatic organic solvents such as benzene, toluene and xylene; and chlorinated aliphatic and aromatic organic solvents such as methylene chloride, chloroform, carbon tetrachloride and chlorobenzene. Preferred organic solvents for carrying out the catalytic hydrogenation of nitrobenzamide (III) are alkanols of one to 6 carbon atoms. Sufficient solvent is employed to provide a concentration of the starting nitrobenzamide (III) of from 5 to 25% by weight.

Suitable hydrogenation catalysts include the noble metals, such as platinum, palladium and rhodium, and Raney Nickel. Preferred hydrogenation catalysts are the supported catalysts such as, for example, platinum on carbon and palladium on carbon. The proportion of catalyst employed is from 1 to 25 parts by weight of reaction mixture.

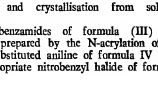
Although any conventional hydrogenation apparatus may be employed, a convenient apparatus provides a low pressure hydrogenation, i.e. one providing from 1 to 100 atmospheres of hydrogen gas pressure. The hydrogenation proceeds satisfactorily at ambient temperatures, i.e. about 25°C., but the rate of reaction may be advantageously speeded by heating the reaction mixture up to about 50°C.

The hydrogen gas pressure employed during hydrogenation is from 1 to 100 atmospheres, and preferably from 2 to 50 atmospheres.

An indication that hydrogenation is complete is the cessation of hydrogen gas consumption. Upon completion of hydrogenation the compound of formula (1) wherein A is amino is separated from the reaction mixture by conventional methods such as filtration to remove catalyst residue, evaporation of

solvent and crystallisation from solvent extracts.

Nitrobenzamides of formula (III) are readily prepared by the N-acrylation of an alkyl substituted aniline of formula IV with an appropriate nitrobenzyl halide of formula V:



(IV) (V)

wherein R_1, R_2 and R_3 are as previously described and X is chlorine, bromine, iodine or fluorine.

The preparation of compounds (III) is carried out by admixture of the reactants (IV) and (V) in substantially equimolar proportions. Preferably the reactants (IV) and (V) are brought together in the presence of an inert organic solvent of the type previously defined. The proportion of inert organic solvent employed is not critical, but preferably is such that the nitrobenzoyl halide (V) is placed in solution. Preferred inert organic solvents are the chlorinated aliphatic and aromatic solvents such as methylene chloride.

The acylation described above proceeds satisfactorily over a broad range of temperature, i.e. from −20°C. to reflux temperature of the particular reaction mixture. In general, the acylation is carried out satisfactorily at temperatures below 150°C. and preferably at from 25°C. to 50°C.

A by-product of the N-acylation reaction described above is the halogen acid corresponding to the particular halide acylating agent. Preferably this halogen acid by-product is removed from the reaction mixture as it forms, and this may be accomplished by conventional methods. For example, an acid acceptor compound such as a tertiary amine may be added to the acylation reaction mixture. Suitable tertiary amines are trimethylamine, triethylamine and tributylamine. The preferred acid acceptor compound is pyridine.

The reaction which occurs during N-acylation is exothermic in nature. The exotherm may be controlled by conventional methods, such as by cooling the reaction mixture. or by the gradual addition of the aniline reactant (IV) to the halide acylating agent (V).

Cessation of continued exotherm is indicative of complerion of the N-acylation. Upon completion of the N-acrylation, the product may be separated from the reaction mixture by conventional methods such as, for example, solvent extraction or crystallisation techniques.

The alkyl-substituted aniline starting compounds of formula (IV) are well known compounds, as is their preparation. Illustrative of the compounds (IV) are *o*-, *m*- and *p*-toluidine; *o*-, *m*- and *p*-ethylaniline; *o*-, *m*- and *p*-isopropylaniline; *o*- *m*- and *p*-*tert*-butylaniline; *o*-, *m*- and *p*-n-pentylaniline; *o*-, *m*- and *p*-n-hexylaniline; 2,6-xylidene, 2,6 - diethylaniline, 3,5-diethylaniline, 2,4-diisopropylaniline, 2,5 - diisopropylaniline and 2 - butyl - 5 - methylaniline.

The nitrobenzoyl halides (V) are also well known, as is their preparation; see for example the method set forth in Acta. Chem. Scand. 14, 2049, (1960). Illustrative of the reactants (V) are *o*- *m*- and *p*-nitrobenzoyl chloride; *o*-, *m*- and *p*-nitrobenzoyl bromide; *o*-, *m*- and *p*-nitrobenzoyl iodide; 2-nitro-*p*-toluoyl cloride; 3 - nitro - 4 - propylbenzoyl chloride, 3 - nitro - 4 - pentylbenzoyl chloride, 3 - nitro - 5 - methylbenzoyl chloride, 3 - nitro - 2 - ethylbenzoyl chloride and 4 - nitro - 2 - hexylbenzoyl chloride.

Compounds of formula I wherein A is —NHY are prepared by acylating compounds of formula I wherein A is amino. The acylation is readily carried out by well known methods, such as by reacting substantially equimolar proportions of the amine and an appropriate hydrocarbon carboxylic acid halide of the formula E—COX (VI) wherein E and X are as defined above. The acylation reaction is advantageously carried out by admixture of the reactants in the presence of an inert organic solvent of the type defined above. Preferred solvents are benzene, diethyl ether, tetrahydrofuran and toluene. The quantity of solvent employed is not critical, but preferably is sufficient to solubilise the reactants.

The acylation of the amines of formula I proceeds satisfactorily at ambient temperatures, but advantageously is carried out at a temperature of from 25°C. to 100°C.

Completion of the acylation may be determined by conventional analytical methods. For example, infra-red analysis will indicate the disappearance of starting materials and the presence of the desired products. On completion of the reaction, the desired product compounds (I) wherein A is a N-acylamino group are separated from the reaction mixture by conventional methods such as, for example, filtration, solvent extraction or crystallisation techniques.

The acid halide compounds (VI) are generally well known and are prepared by a wide variety of known methods; see for example, Rodd, Chemistry of Carbon Compounds, Elsevier Pub. Co., N.Y., Vol. Ia, p. 588 and Vol. IIIa, p. 547 (1951). One method is by reaction of an appropriate hydrocarbon carboxylic acid with a phosphous halide such as phosphorus pentachloride or phosphorus tribromide. Examples of appropriate hydrocarbon carboxylic acids are listed above.

Examples of the acid halides (VI) are acetyl chloride, propionyl chloride, isobutryl chloride, valeryl chloride, isovaleryl chloride, neopentylacetyl chloride, hexanoyl chloride, heptanoyl chloride, stearoyl chloride, palmitoyl chloride, phenylacetyl chloride, benzoyl chloride, *o-* *m-* or *p-*tolyl chloride, cyclopentanepropionyl chloride, cyclohexaneacetyl chloride, acryloyl chloride, crotonyl chloride, 2-hexynoyl chloride and 2-octynoyl chloride.

An alternative method of preparing the compounds of the invention from the intermediate amines is by the method of Chu, J.A.C.S., 67, 1862—3, which comprises employing the anhydride of the carboxylic acid as the acylating agent i.e. a compound of formula YOY instead of YX.

An alternative method of preparing the compounds of the invention in which the amino or —NHY group is at the 2-position, is by (1) reacting a compound of the formula

wherein R_1 is as defined above, with a compound of the formula

wherein R_2 and R_3 are as defined above, and, if desired (2) acylating the product of step (1) with a chloride of the formula YCl or an anhydride of the formula YOY, Y being as defined above.

By way of example by repeating Example 1 of Application No. 14543/74 but using 0.1 mole of *o* - nitrobenzoyl chloride instead of the 2 - nitro - *m* - tolyoyl chloride, 2 - nitro - 2',6' - benzoylidide is obtained.

If 0.067 moles of the above product is then substituted for the 2 -nitro - *m* - tolu - 2',6' - xylidide used in Example 2 of Application No. 14543/74, Serial No. 1459141, 2 - amino - 2',6' - benzoxylidide is obtained.

The compositions of the invention can suitably be formulated to provide an effective amount of the active ingredient, in solid or liquid forms for oral, rectal or parenteral administration to control convulsions and seizures in mammals. Preferably the compositions are provided with a sterile liquid carrier for oral or parenteral administration or with a solid carrier for oral or rectal administration.

Compositions intended for oral use are tablets, aqueous or oily suspension, powders, granules, emulsions, syrups, elixirs or capsules, the preparation of which is well known. Such compositions may contain one or more sweetening, flavoring, coloring or preserving agents to provide an elegant and palatable pharmaceutical preparation.

The solid oral forms, in addition to containing the essential active ingredient may contain, additionally, suitable pharmaceutical carriers, i.e., excipients, such as inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch or alginic acid; binding agents such as starch, gelatine or acacia; or lubricants such as magnesium stearate, stearic acid or talc.

Tablet forms may be uncoated or coated, by known methods, to provide sustained release of the active ingredient over a prolonged period of time, i.e., enterically coated.

Dispersible powder and granule forms, such as freeze dried forms suitable for extemporaneous preparation of an aqueous suspension, by the addition of a fluid carrier containing active ingredient, may be compounded with dispersing, wetting, suspending and preserving agents.

Properly formulated by methods known in the art, many of the oral solid forms may be administered rectally. Preferably, however, the compositions of the invention for rectal use are prepared by mixing the essential active ingredient with a pharmaceutically acceptable non-irritating excipient which is solid at ordinary room temperatures but liquid at rectal temperature. Illustrative of such excipients are cocoa butter and polyethylene glycols. The mixed composition is then cast in the form of a rectal suppository.

Aqueous suspensions of the essential active ingredient for oral administration are prepared, for example, by admixture with pharmaceutically acceptable carriers, i.e., excipients such as suspending agents like methylcellulose, gum acacia, gum tragacanth or sodium carboxymethylcellulose; preservatives, flavoring and sweetening agents.

Parenteral compositions of the invention are prepared by conventional methods, i.e., as sterile injectable aqueous suspensions which may contain in addition to active essential ingredient, pharmaceutically acceptable wetting, buffering, pH adjusting, dispersing, suspending and preserving agents. The parenteral compositions of the invention may be administered intramuscularly, subcutaneously or intraperitoneally.

Each of the pharmaceutical forms which comprises the composition of the invention are preferably formulated so as to provide from 25 mg. to 250 mg. of the active compound per unit dose. Each dose is administered, generally, from 1 to 4 times a day so as to provide a total daily dose of from 25 mg. to 1 g. with single dosages ranging from 25 mg.

to 250 mg. The dosage can, of course, be adjusted by the attending physician with respect to age, weight, and affliction of the recipient being treated.

The following Examples are illustrative of the compositions of this invention. The active ingredient used in each is 2 - amino - 2',6' - benzoxylidide.

Example 1

Aqueous oral suspension

An aqueous oral suspension is prepared from the following constituents:

active ingredient	2.5 gm.
microcrystalline cellulose	1.1 gm.
sodium carboxymethylcellulose	0.9 gm.
orange flavour	0.45 gm.
sterile water q.s.	100 ml.

The microcrystalline celluluse is dispersed in the water, and the sodium carboxymethylcellulose and orange flavour are added and dissolved by means of a high shear mixer. The active ingredient is added and the suspension homogenized.

The composition can be given as one or two teaspoons (5 ml.), daily.

Example 2

Tablets

A lot of 10,00 tablets, each containing 100 mg. of the active ingredient, is prepared from the following constituents:

active ingredient	1,000 gm.
dicalcium phosphate	1,500 gm.
methylcellulose, U.S.P. (15 cps)	60 gm.
talc	150 gm.
corn starch	200 gm.
calcium stearate	12 gm.

The active ingredient and dicalcium phosphate are mixed well, granulated with a 7.5% solution of methylcellulose in water, passed through a No. 8 screen and dried carefully. The dried granules are passed through a No. 12 screen, mixed thoroughly with talc, starch and calcium stearate, and compressed into tablets.

One or two of these tablets can be given to a suitable subject, per day.

Example 3

Suppository

One thousand suppositories, each weighing 2.5 gm. and containing 100 mg. of active ingredient, for rectal administration, are prepared from the following constituents:

active ingredient	100 gm.
propylene glycol	165 gm.
polyethylene glycol 4000 q.s.	2,500 ml.

The active ingredient is added to the propylene glycol and dispersed. The polyethylene glycol 4000 is melted and added to the dispersion. The suspension is poured into moulds and cooled to allow solidification. These suppositories can be administered at a dose of 1 suppository, 1 to 3 times a day.

Example 4

Parenteral Aqueous Suspension

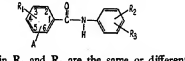
A sterile aqueous suspension for parenteral administration and containing 50 mg. of active ingredient per ml. is prepared from the following constituents:

active ingredient	50 gm.
polysorbate 80	8 gm.
sodium chloride	18 gm.
benzyl alcohol	18 gm.
sterile water for injection q.s.	1,000 ml.

A suitable dosage is 1 to 2 ml. daily.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising, as an active ingredient, an aminobenzamide, in association with a pharmaceutically acceptable sterile liquid or solid carrier, in which the aminobenzamide is a compound of the formula



wherein R_1 and R_2 are the same or different and are each hydrogen or lower alkyl; R_3 is lower alkyl; and A is amino or a monovalent group of the formula —NHY wherein Y is the acyl radical of a hydrocarbon carboxylic acid having from 2 to 18 carbon atoms, with the provisos that

(i) when R_1 is hydrogen, A is not 4-amino or 2-NHY;

(ii) when R_1 is alkyl, A is amino; and

(iii) when R_1 is 3-methyl, A is not 2-amino.

2. A composition according to claim 1 in a form suitable for oral administration and in which the carrier is a sterile liquid.

3. A composition according to claim 1 in a form suitable for parenteral administration and in which the carrier is a sterile liquid.

4. A composition according to claim 1 in a form suitable for oral or rectal administration and in which the carrier is a solid.

5. A composition according to claim 4 in unit dosage form and in which each unit

dosage contains from 25 to 250 mg. of the active ingredient.

6. A composition according to claim 1 substantially as herein described with reference to the Examples.

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